Subst. E3

19. (Amended) A method for protecting an animal against a papillomavirus infection, said method comprising administering a therapeutically effective amount of a vaccine, wherein said vaccine comprises at least one PV type of recombinantly produced L1 protein or antigenic fragment[s] thereof, which is capable of [substantially] reproducing the antigenicity of the L1 major capsid protein expressed on the surface of intact papillomavirus virions.

N.E 1.121

In claim 41, line 4, delete "substantially" and after "antigenicity of" insert --the L1 major capsid protein exposed on the surface--.

REMARKS

Entry of the foregoing amendments are respectfully requested, as well as consideration of the three unexecuted § 1.132 Declarations which are submitted with this Reply. The executed declarations will be furnished to the Examiner upon receipt by Applicants' representative.

By the present amendments, the independent claims have been amended to delete "substantially" in favor of language reciting that the recombinant L1 protein reproduces the antigenicity of the L1 major capsid protein expressed on the surface of intact papillomavirus virions. Thus, it should now be abundantly clear that the expressed protein reproduces the native antigenicity of the L1 protein and not other papillomavirus proteins as asserted by the Examiner. However, it is still respectfully argued that the previous claim phraseology was accurate and not indefinite since the L1 major capsid

protein is the papillomavirus protein which is the dominant immunogenic protein expressed on the surface of papillomavirus. Accordingly, contrary to the position taken by the Examiner, the subject recombinant L1 proteins do, in fact, substantially reproduce the antigenicity of intact papillomavirus viruses. However, in any event, the new claim phraseology should render this issue moot since there is convincing evidence of record that the subject recombinant L1 proteins reproduce the antigenicity of the L1 major capsid protein (since these proteins have been demonstrated to react with conformationally specific anti-L1 proteins monoclonal antibodies).

Turning now to the §132 declarations submitted with this Preliminary Amendment, it is respectfully submitted that these three declarations, taken cumulatively, should be sufficient to obviate all of the outstanding §103, §112 and §101 rejections. In particular, the two expert declarations by Jeffrey Cossman and Gary Pearson, both of which are Department Chairmen at Georgetown University School of Medicine contain the opinions of two respected experts in the art. Both of these experts independently reviewed the subject application and references cited therein, as well as the additional experimental data contained in the third declaration by Richard Schlegel (an inventor of this application) and independently concluded that one highly skilled in the art, given the teachings in this application, would be able to practice the claimed invention absent undue experimentation. Moreover, both experts concluded that the *in vitro* and *in vivo* evidence contained in the subject application and in the Schlegel §132 declaration, to comprise convincing evidence that the subject recombinant papillomavirus capsid proteins may be used as an effective vaccine for protecting a susceptible host against a homologous

papillomavirus (i.e., a papillomavirus which expresses the particular L1 protein). It is further noted that both experts further assert that the two *in vitro* assays described in the subject application (xenograft and C127 cell neutralization assay) comprise art recognized assays for predicting the *in vivo* efficacy of papillomavirus proteins for inducing papillomavirus neutralization and immunity.

Additionally, both of these experts independently reviewed the art of record, and concluded that one skilled in the art they would not have reasonably concluded based on the cited references that recombinant L1 proteins could be expressed in conformationally correct form, or that such proteins could be used as an effective vaccine for affording immunity against papillomavirus infection. It should be noted that while scientific experts are not permitted to give opinions concerning the ultimate obviousness issue (since they are scientific and not legal experts), those opinions providing compelling evidence that experts in the art did not find the claimed invention to be of a routine nature. The non-routine nature of the claimed invention finds further support in the collective opinion of the expert committee who reviewed the Schlegel NIH grant application corresponding to this invention. These comments are contained in the attachment to the Schlegel Declaration. In particular, please note the last full paragraph on page 3, wherein the 24 experts expressed their collective opinion that recombinant L1 protein expressed in COS cells might not be able to induce a sufficient immunogenic response to stimulate papillomavirus neutralization.

Finally, the §132 Declaration by Richard Schlegel provides incontrovertible evidence that recombinant conformationally correct papillomavirus L1 proteins may be

used to induce an effective, protective immune response in a susceptible host. The Schlegel declaration contains additional experiments relating to COPV, a canine papillomavirus which is highly related to human papillomaviruses (e.g., these viruses share antigenic epitopes, and both are mucosotropic). In the Schlegel declaration, it was demonstrated that administration of recombinant COPV L1 proteins produced in eukaryotic cells according to the invention to beagles resulted in 100% protection upon challenge with infectious COPV. By contrast, all dogs which were not administered the COPV L1 protein became infected after challenge with COPV. These results therefore provide convincing *in vivo* evidence that recombinant L1 proteins provide an effective vaccine for affording protection against papillomavirus, and specifically against COPV and HPV given the substantial relatedness of these viruses. It is further noted (as discussed in the §132 declarations) that an FDA official has indicated to one of the present inventors (Bennett A. Jenson) that the *in vivo* data relating to COPV would be probative concerning the potential efficacy of conformationally correct HPV L1 proteins for conferring protection against papillomavirus infection.

It is additionally noted, as discussed in Applicants' Reply filed on June 10, 1993 and in the Schlegel §132 declaration, that evidence is contained in the subject application which demonstrates that recombinant HPV L1 proteins produced according to the invention are obtained in conformationally correct form. This was established by the fact that the recombinantly produced HPV-1 L1 proteins expressed in COS cells immunoreacted with a number of different monoclonal antibodies, each of which antibodies recognize particular HPV-1 conformational epitopes. Additionally, the

expressed HPV-1 L1 protein was intranuclearly localized, which provides further evidence that the recombinant L1 protein was processed and translocated equivalently as this protein is expressed on intact papillomavirus viruses. (These results may be found in Example 2 at pages 37-40 of this application). Therefore, given the results obtained with the recombinant COPV L1 protein contained in the Schlegel declaration, it is reasonable to assume that recombinant HPV L1 proteins, which are expressed in conformationally correct form, will likewise comprise applicability in the design of (human) papillomavirus vaccines.

Thus, based on the foregoing remarks, and further based on the opinion and experimental evidence contained in the three §132 declarations submitted herewith, favorable consideration of the claimed invention is respectfully requested.

However, if the Examiner after consideration of the § 1.132 Declarations and the new evidence contained therein finds this new evidence to be non-convincing to rebut the rejections, it is respectfully requested that he contact the undersigned so that a personal interview may be scheduled. This will enable Applicants interview the Examiner so that any outstanding issues may be resolved, either by appropriate amendments or by the submission of additional evidence. It is believed that a request for interview prior to first

Office Action is not premature given that this application is a file-wrapper continuation application, and further because it will allow Applicants the necessary time to obtain additional evidence, should such additional evidence be required by the Examiner.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS

By: _____
Donna M. Meuth
Registration No. 36,607

The George Mason Building
Washington & Prince Streets
Post Office Box 1404
Alexandria, VA 22313-1404
Phone: (703) 836-6620

Date: June 6, 1994